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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/821,726	03/29/2001	Terence Martin	21459/90913	5474

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EXAMINER
SULLIVAN, DANIEL M

ART UNIT	PAPER NUMBER
1636	16

DATE MAILED: 10/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/821,726	MARTIN ET AL.	
	Examiner	Art Unit	
	Daniel Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *12,16-21 and 23-26* is/are withdrawn from consideration.

5)☐ Claim(s) ~~*1-11,13-15,22 and 27-29*~~ is/are allowed.

6)☒ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This is a First Office Action on the Merits of the application filed March 29, 2001. The Information Disclosure Statement, filed October 1, 2001, and preliminary amendments A (filed October 26, 2002; paper #12) and B (filed June 18, 2002; paper #14) have been entered. Claims 1-29 are pending in the application.

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-11, 13-15, 22, 27 and 28 in Paper No. 15 is acknowledged. Applicant has also requested that claim 29 be examined with the elected claims. The claim is clearly encompassed within the elected group and will therefore be rejoined with Group I for examination.

Claim Objections

Claims 2-4 and 7-10 objected to because of the following informalities: the claims are drawn to amino acid sequence but do not provide a sequence identifier number. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5, 6, 11 13-15, 22 and 27-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The claims are drawn to a group of isolated homologous growth stimulating proteins produced by gastric epithelial cells and comprising the amino acid sequence VKEKKKXXGKGPGGXPPK or VKEQKKXXGKGPGGXPPK, derivatives and modifications of said growth stimulating proteins and methods of using said growth-stimulating proteins. Given their broadest reasonable interpretation, the claims encompass a genus made up of any and all proteins produced by gastric epithelial cells and comprising the indicated sequence that are capable or stimulating cellular growth, as well as methods of using that genus of proteins. The Revised Interim Guidelines state "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus", "In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Column 2, page 71436). The written description requirement for a claimed genus may be satisfied through sufficient

description of a representative number of species, by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics (see MPEP 2163 (ii)).

The specification describes human and porcine proteins comprising the amino acid sequence VKEKKLQGKGPGGPPPK and a murine protein comprising the amino acid sequence VKEQKGKGPGGAPPK (see especially Figure 10). The specification also describes several synthetic fragments comprising portions of the murine, porcine or human sequence and reduction to practice of growth stimulation in a tissue culture system. The specification does not describe any proteins comprising the amino acid sequences VKEKKKXXGKGPGGXPPK or VKEQKKXXGKGPGGXPPK outside of claim 1 and there is no reduction to practice of a protein comprising these sequences. The sequence set forth in claim 1 appears to have been created by combining features of the human/porcine peptide with features of the murine peptide to arrive at the insertion of K or Q at position four, and the insertion of any amino acid at positions 7, 8 and 15. Although the structure of these peptides is described in the claim, nowhere does the disclosure demonstrate that the described peptide has growth stimulating activity or that proteins comprising this sequence are produced by gastric epithelial cells.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention, as the disclosure does not describe a single protein comprising the peptide set forth in claim 1 and having the functional characteristics also set forth. Therefore, the claims do not meet the written description provision of 35 U.S.C. §112, first paragraph.

Claims 1, 5, 6, 11, 13-15, 22 and 27-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

The application describes proteins produced by mouse, pig and human gastric epithelium that are capable of stimulating the growth of epithelial cells in tissue culture, and fragments of the proteins that retain the ability to stimulate cell growth. The metes and bounds of the claims are set forth above. The art teaches that the effect of inserting, deleting or substituting amino acids in proteins is highly unpredictable. Clackson and Wells (*Science* (1995) 267:383-386), for example, teach that "[a] number of crystallographic studies have shown that the binding interfaces between proteins are generally large... and include many intermolecular contacts, involving 10 to 30 side chains from each protein...However, structural analysis alone cannot show whether all of these contacts are important for tight binding. A complete understanding of the chemistry of protein-protein association also requires a functional map of each binding surface, to reveal to what extent each contact contributes to the overall free energy of binding" (page 383, first paragraph of the Clackson and Wells article). This teaching points out the

unpredictability of assigning functional consequences to structural modifications without empirical experimentation. The disclosure provides the structure of related human, mouse and pig proteins and identifies a functional region within these proteins by reduction to practice of growth stimulation by said functional region in tissue culture. The disclosed functional peptides comprise either one of the following sequences: VKEKKLQGKGPGGPPPK or VKEQGKGPGGAPPK. The claims, however, encompass a functional protein comprising the amino acid sequence VKE*X*KKXXGKGPGGXPPK or VKE*Q*KK*XX*GKGPGG*X*PPK, wherein X can be any amino acid. Neither the disclosure nor the prior art have attributed a function to a protein comprising the insertion of a lysine or glutamine at position four of the functional peptide and the disclosure only teaches functional peptides comprising leucine-glutamine at position six-seven, and proline or alanine at position fourteen (numbered according to the human sequence). Therefore, the skilled artisan seeking to make the invention would have to engage in empirical experimentation to identify proteins produced by gastric epithelium with the claimed structural features and capable of stimulating growth or would have to derive such a protein. Based on the teachings of the specification, one would not be able to predict either the existence of the claimed protein or the likelihood of success in producing such a protein with the requisite biological activity. Therefore, making and using the claimed invention would place an undue burden on the skilled artisan.

Claims 13-15, 22 and 27-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention.

The nature of the invention is described above. Claims 13-15 are drawn to a composition for the treatment of ulcers, ulcerative colitis, Crohn's Disease, or diseases associated with overgrowth of the gastric epithelia comprising either a growth stimulating peptide or an inhibitor thereof according to the peptides and proteins of the instant application. Claims 22 and 27-29 are drawn to methods of stimulating growth and migration of epithelial cells in the gastrointestinal tract of mammals and a method for cytoprotection of damaged epithelial cells in the gastrointestinal tract of mammals. The relevant prior art as exemplified by Tarnawski (1997) *Drugs of Today* 33:697-706) teaches that healing of the gastric and intestinal mucosa is a complex integrated process. Tarnawski teaches that dedifferentiation and proliferation of epithelial cells in the process of healing an ulcer "is the result of local activation of genes encoding for epidermal growth factor (EGF), its receptors and likely other growth factors, such as hepatocyte growth factor (HGF), trefoil growth peptides (TGP), transforming growth factor (TGF-β) and basic fibroblast growth factor (bFGF)" (page 697, paragraph 1) and that "[t]he final outcome of the healing process reflects a dynamic interaction between the epithelial cells from the healing zone at the ulcer margin and the connective tissue cells...Depending on these interactions, mucosal scar can be of good quality...or poor quality" (second paragraph of column 2). These teachings indicate that the effect of administering a composition comprising the growth stimulatory peptide, or inhibitor thereof, on healing processes in the gastric epithelium is unpredictable because the outcome of the healing process is dictated by a disparate set of determinants. Additional uncertainty comes from the teachings of Schassmann *et al.* (1997)

Gastroenterology 113:1858-1872, who examined the effects of exogenously applied HGF in an animal ulcer model. In attempting to explain the lack of efficacy of HGF in the treatment of early phase of healing Schassmann *et al.* teach, "[f]irst exogenous rhHGF competes with strongly up-regulated endogenous HGF, which acts by both a paracrine and an endocrine pathway. Second, the microvascular system in the ulcer crater is poorly developed on day 3; thus, parenterally administered exogenous rhHGF may not sufficiently reach the HGF receptor Met in the ulcerated region. Third, rhHGF may be inactivated by acid-pepsin damage" (beginning on page 1869, first full paragraph and continued through the first paragraph on page 1870). Any one of these factors might also limit or block efficacy of the disclosed proteins or peptides in a similar manner.

To date, there is no teaching of the clinically successful use of a growth stimulatory or growth inhibitory peptide in the treatment of the named conditions. In the absence of any such teaching, the skilled artisan must rely on the instant disclosure to provide sufficient guidance to use the invention without undue experimentation. The teachings of the specification are limited to tissue culture and almost exclusively to kidney epithelial cells. On page 31, lines 26-30, the specification provides that an adenocarcinoma cell line obtained from stomach and a non-transformed rat intestinal epithelial cell line responded to the AMP-18 peptides. There is, however, no evidence provided that administering the described AMP-18 peptides or proteins has any effect on healing of ulcers *in vivo*. In fact, there is no evidence provided to indicate that intestinal epithelial cells in the region of an ulcer, *in vivo*, express a AMP-18 receptor. The disclosure provides no guidance as to how a AMP-18 peptide or protein, or inhibitor thereof, should be administered, or how much should be administered, in order to achieve a therapeutic

effect. With regard to the use of an antagonist as a therapeutic, there is no evidence provided that would indicate that activation of the putative AMP-18 receptor contributes to a pathological state. Therefore, the teachings of the specification do not even instruct the skilled artisan as to which patient population should receive the inhibitor.

With regard to growth, migration and cytoprotection, both of the cited references teach that expression of growth factor receptors in the gastrointestinal tract is dynamic. Schassmann *et al.* teaches that, "changes in receptor densities have been shown and have been reported to be involved in ulcer healing" (first paragraph of page 1858) and Tarnawski teaches that, "mucosal ulceration triggers activation of genes encoding for growth factors and their receptors" (page 699, first paragraph of column 1). These teachings, and teachings from the specification that not all cells respond to AMP-18 (page 19, line 20) raise the possibility that expression of the receptor for AMP-18, or responsiveness to AMP-18, *in vivo* could vary depending upon the location within the gastrointestinal tract, or depending upon the health or status of the cells. Due to this uncertainty in the art, the skilled artisan is dependent upon the specification to teach how to perform the method without undue experimentation. As discussed above, the disclosure does not provide guidance as to when or where the AMP-18 receptor is expressed *in vivo* and thus the skilled artisan would have to engage in empirical experimentation to identify cells in the gastrointestinal tract of mammals that respond to AMP-18 in order to practice the method. Also described above, the skilled artisan must engage in empirical experimentation to identify an effective concentration and route of administration of the AMP-18 in order to practice the invention.

Given the high degree of uncertainty in the art regarding how to treat of ulcers and diseases involving overgrowth of the gastric epithelium using agents with properties similar to the disclosed AMP-18 proteins and peptides, and the failure of the specification to provide guidance as to how the claimed compositions could be used, even in animal models of human disease, the skilled artisan would have to engage in undue experimentation in order to learn how to use the claimed invention. This would place an undue burden on one seeking to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11, 13-15, 22 and 27-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 5, 6, 13-15, 22 and 27-29 are drawn to a products and methods comprising a group of isolated *homologous* cellular growth stimulating proteins. The claims are indefinite because the metes and bounds of the term "homologous" are not set forth in the disclosure. It is therefore unclear what is included or excluded from the claimed subject matter according to the limitation.

Regarding claim 11, the claim recites a peptide comprising a gap of indeterminate length. Although it appears that Applicants intention is that the claim is drawn to the peptide of SEQ ID NO:2, the fact that the sequence provided in the claim is different from the sequence of SEQ ID

NO:2, in that it comprises a gap, renders the claim indefinite. This rejection can be traversed by simply removing the peptide sequence from the claim so that the claim is drawn to SEQ ID NO:2.

Claims 2, 3, 4 and 7-11, are also indefinite because there is insufficient antecedent basis in claim 1 for the claimed proteins or peptides. Claim 1 is drawn to a protein comprising the sequence 'VKEKKKXXGK...' or 'VKEQKKXXGK...', the sequences of the dependent claims comprise only the sequence 'VKEKKXXGK...' or 'VKEQKGXXP...'.

Claim 2 is also indefinite in that it is drawn to an isolated protein while the figure to which it refers (Fig. 7) sets forth a nucleic acid sequence. In the interest of compact prosecution, the claim has been examined on the merits with the assumption that Applicant intends that it be drawn to the amino acid sequence set forth in Figure 18.

Claim 3 is also indefinite because it is drawn to an isolated protein comprising the sequence set forth in Figure 8, which is 185 amino acids long, and further limited to a 165 amino acid processed form within the same claim. It is not clear whether the claim is to be limited to a protein comprising the 185 amino acid unprocessed form or the 165 amino acid processed form. In the interest of compact prosecution, the claim has been examined according to its broadest reasonable interpretation as being drawn to an isolated protein comprising the 185 amino acid sequence set forth in Figure 8.

Claims 7-11 are indefinite in their being drawn to a "synthetic growth stimulating peptide". Synthetic AMP-18 peptides are described in "16. AMP-18 related synthetic peptides" beginning on page 28. The definition of synthetic is not, however, explicitly set forth and it is not clear whether Applicant intends that the term limit the structure of the peptide (i.e. not found in nature) or the method of manufacture (i.e. chemical, as opposed to biological, synthesis).

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 4 and 11 are rejected under 35 U.S.C. 102(a) as being anticipated by Hayashizaki *et al.* (8 February 2001) *Nature* 409:685-690.

Claim 4 is drawn to a protein comprising an amino acid sequence set forth in the instant application in Figure 6 and claim 11 is drawn to a bioactive peptide comprising a sequence set forth in the instant application as SEQ ID NO:2. Hayashizaki *et al.* teach a protein comprising an amino acid sequence identical to the sequence set forth in Figure 6 (see the attached sequence alignment) and comprising the sequence set forth as SEQ ID NO:2 (compare positions 97-118). The protein taught by Hayashizaki *et al.* is the same as the protein taught in the instant application, therefore the limitations of the claims are met by Hayashizaki *et al.*

Claims 2, 3 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Powell (1987) IDS #BQ or Jacobs *et al.* (1999; WO 99/07840).

Claims 2 and 3 are drawn to an isolated protein comprising the amino acid sequences set forth in Figures 8 and 3, respectively. Claim 11 is drawn to an isolated bioactive peptide comprising the sequence set forth in the instant application as SEQ ID NO:3. In Figure 18, page 155, Powell teaches an amino acid sequences for human and porcine proteins that are identical to the sequence taught in Figures 8 and 3 of the instant application and comprising, at positions

104-117, the sequence set forth in the instant application as SEQ ID NO:3. The proteins and bioactive peptide taught by Powell is the same as the claimed proteins and peptide.

Claims 3 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Jacobs *et al.* (1999; WO 99/07840).

The limitations of the claims are recited above. Jacobs *et al.* teaches an amino acid sequence that is identical to the sequence taught in Figure 3 of the instant application and comprising, at positions 104-117, the sequence set forth as SEQ ID NO:3 (see especially the sequence set forth in Jacobs *et al.* as SEQ ID NO:18). The protein and bioactive peptide taught by Jacobs *et al.* are the same as those taught in the instant application; therefore the claims are anticipated by the prior art

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
September 24, 2002

JAMES KETTER
PRIMARY EXAMINER